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CLONED POTASSIUM CHANNELS FROM EUKARYOTES AND PROKARYOTES

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ABSTRACT

Potassium channels contribute to the excitability of neurons and signaling in the nervous system. They arise from multiple gene families including one for voltage-gated potassium channels and one for inwardly rectifying potassium channels. Features of potassium permeation, channel gating and regulation, and subunit interaction have been analyzed. Potassium channels of similar design have been found in animals ranging from jellyfish to humans, as well as in plants, yeast, and bacteria. Structural similarities are evident for the pore-forming α subunits and for the β subunits, which could potentially regulate channel activity according to the level of energy and/or reducing power of the cell.

INTRODUCTION

Potassium channels are ubiquitous in the animal and plant kingdoms and in yeast and bacteria (Hille 1992); they exhibit extraordinary heterogeneity among these organisms while preserving several salient features. These potassium channels contribute to the control of potassium flow, cell volume, release of hormones and transmitters, resting potential, and excitability of neurons and muscles.

Potassium channels may be regulated by changes in the membrane potential or the metabolic state of the cell, or by transmitters and hormones (Hille 1992). Such regulation contributes to signaling between neurons and mechanisms for cellular protection during stressful events, such as anoxia and ischemia. Indeed,

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pharmacological reagents that decrease or increase potassium channel activity have been characterized as potential anti-ischemic, antiarrhythmic, antihypertensive, or anti-anginal agents as well as for treatment of bladder detrusor instability (Lynch et al 1992, Katz et al 1993, Grover 1994, Olesen 1994, Li et al 1995, Quast et al 1995). Venoms from snake, bee, scorpion, sea anemone, and marine snail often contain toxins that block potassium channel function (Stansfeld et al 1987, Castle et al 1989, Hurst et al 1991, Miller 1995).

The physiological significance of potassium channel function is also evident from pathological consequences of mutations of potassium channels and their associated proteins. Mutations of potassium channel genes have been associated with neurological diseases, such as the episodic ataxia/myokymia syndrome (Browne et al 1994, Adelman et al 1995), and cardiac arrhythmia (Curran et al 1995, Sanguinetti et al 1995). Mutations in the gene for the sulfonylurea receptor, a β subunit of the ATP-sensitive potassium channel in the pancreas, segregate with familial persistent hyperinsulinemic hypoglycemia of infancy (Inagaki et al 1995, Thomas et al 1995). In mice, hypomyelination in the *shiverer* mutant is accompanied with an up-regulation of voltage-gated potassium channel expression, perhaps as a compensatory mechanism to improve impulse conduction (Wang et al 1995), and a point mutation in a G-protein-gated inwardly rectifying potassium channel gene is associated with the *weaver* mutant with abnormal differentiation of cerebellar neurons and dopaminergic neurons (Patil et al 1995, Slesinger et al 1996). Indeed, behavioral and electrophysiological abnormalities caused by mutations in various voltage-gated potassium channel genes in *Drosophila* have led to the cloning of these genes and their homologs in other species (Jan & Jan 1992, Ganetzky et al 1995).

Cloning of potassium channel genes using molecular genetic methods and expression cloning has led to the identification of two large families of potassium channels: voltage-gated potassium channels and inwardly rectifying potassium channels (Figure 1). Voltage-gated potassium channels and the related calcium-activated potassium channels contain six putative transmembrane segments (S1–S6) in each α subunit (Jan & Jan 1992, Pongs 1992, Chandy & Gutman 1995). Known β subunits of voltage-gated potassium channels contain a potential NAD(P)H-binding motif but lack any membrane-spanning sequences (Scott et al 1994, McCormack & McCormack 1994, Rettig et al 1994), whereas the β subunit of calcium-activated potassium channels (maxi K) contains two putative transmembrane segments (Knaus et al 1994, Wallner et al 1995). Inwardly rectifying potassium channels appear to be distantly related to voltage-gated potassium channels and contain only two putative transmembrane segments (M1, M2) in each α subunit (Jan & Jan 1994, Doupnik et al 1995). The β subunit of an inwardly rectifying potassium channel, the ATP-sensitive potassium channel, contains multiple putative transmembrane segments and two

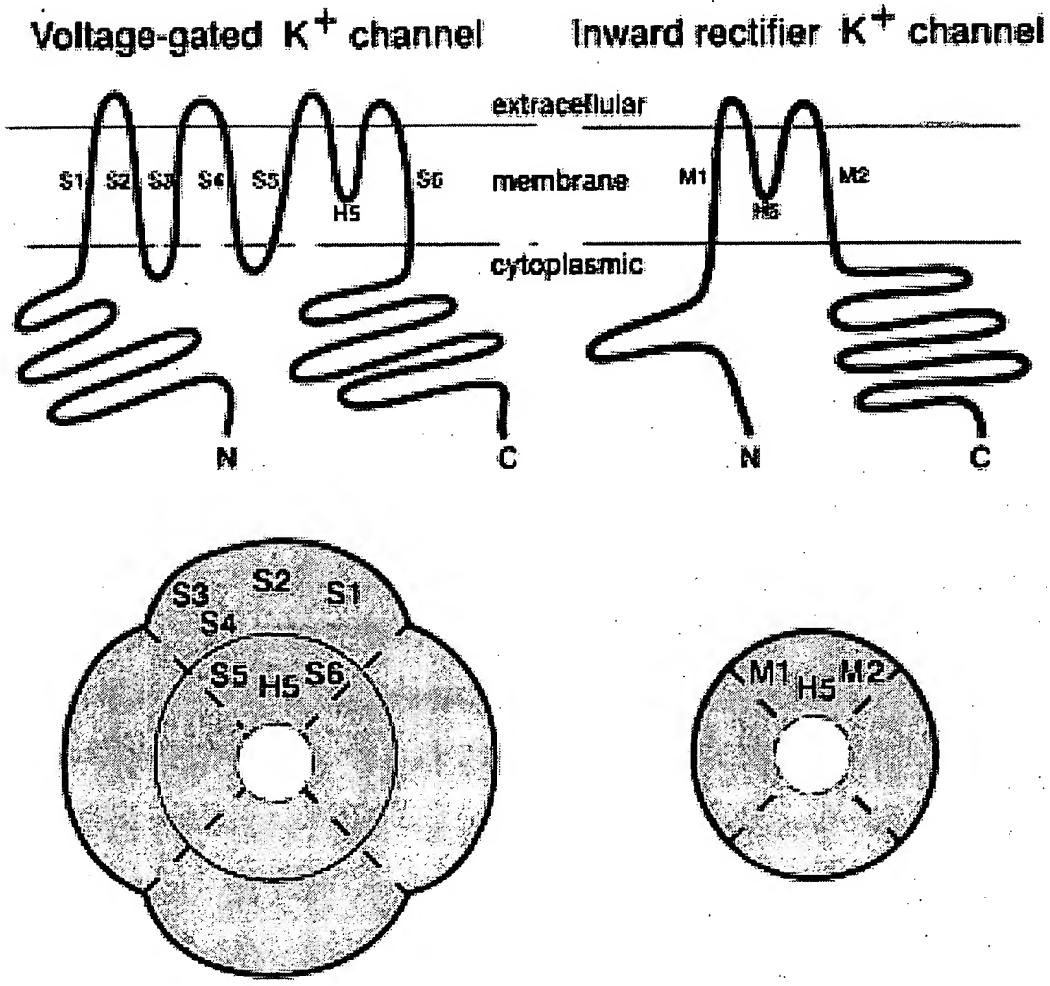

Figure 1 Proposed membrane topology of voltage-gated potassium channel and inwardly rectifying potassium channel. Compared with the voltage-gated potassium channel, which may contain an outer shell of S1, S2, and S3 segments as well as the S4 segment functioning as part of the voltage sensor, the inwardly rectifying potassium channel represents a more reduced structure corresponding to the inner core of the voltage-gated potassium channel. (From Kubo et al 1993a.)

nucleotide-binding domains, and belongs to the ATP-binding cassette (ABC) superfamily (Aguilar-Bryan et al 1995). This review summarizes recent analyses of these two families of potassium channels in the animal kingdom, and related channels in plants, yeast, and bacteria.

VOLTAGE-GATED POTASSIUM CHANNELS

The presence of intrinsic voltage sensors in voltage-gated potassium channels allows the activity of these channels to be controlled by membrane potential and enables them to control the waveform and firing patterns of action potentials

(Hille 1992). At least 18 genes for voltage-gated potassium channel α subunits are known to be expressed in the mammalian nervous system. These genes belong to six subfamilies, corresponding to six *Drosophila* potassium channel genes (mammalian channels in parentheses): *Shaker* (Kv1.1–1.7), *Shab* (Kv2.1, 2.2), *Shaw* (Kv3.1–3.4), *Shal* (Kv4.1–4.3), *ether-a-go-go* or *eag* (HERG), and *slowpoke* or *slo* (maxi K) (Wei et al 1994, Chandy & Gutman 1995, Trudeau et al 1995). Some channels in the *Shaker* subfamily contain four α subunits and four β subunits (Scott et al 1994).

Potassium Permeation

How does a potassium channel discriminate between potassium ions and other monovalent cations such as sodium, and at the same time allow potassium ions to go through the channel pore in less than one microsecond? Extensive biophysical studies have revealed that a potassium channel has a long pore that accomodates multiple potassium ions in single file (Hille & Schwarz 1978, Neyton & Miller 1988, Shapiro & DeCoursey 1991). While the individual potassium-binding sites in the channel pore may show much higher affinity for potassium than sodium, the presence of multiple potassium ions in the channel pore may facilitate their dissociation from the binding sites by electrostatic repulsion.

The multi-ion nature of the *Shaker* voltage-gated potassium channel has been established based on the following findings: (*a*) The permeability ratios for two different permeant ions depend on the ion concentrations (Perez-Cornejo & Begenisich 1994). (*b*) The single channel current carried by potassium and ammonium ions is a nonmonotonic function of the mole fraction of these two ions in the solution (called the anomalous mole fraction effect) (Heginbotham & MacKinnon 1993). (*c*) Two barium-binding sites have been found (Hurst et al 1995). (*d*) The voltage dependence of the cesium block of the channel pore varies with cesium concentration (Pérez-Cornejo & Begenisich 1994). (*e*) Channel blocking by tetraethylammonium (TEA) depends on the concentration of TEA on the other side of the membrane (Newland et al 1992). (*f*) The ratio of potassium influx and efflux has an Ussing flux ratio exponent of 3.4, indicating that at least four potassium ions may be present in single file in a channel pore (Stampe & Begenisich 1996).

Consistent with the multi-ion nature of the *Shaker* voltage-gated potassium channel, several structural elements have been found to be involved in potassium permeation (Figure 2): the S4-S5 loop that interacts with permeant ions as well as the inactivation particle (the ball) from the cytoplasmic side of the membrane, thereby allowing the ball to occlude the channel pore (Isacoff et al 1991, Slesinger et al 1993), the S6 segment that also contributes to the inner portion of the pore (Choi et al 1993, Aiyar et al 1994, Lopez et al 1994, Taglialatela

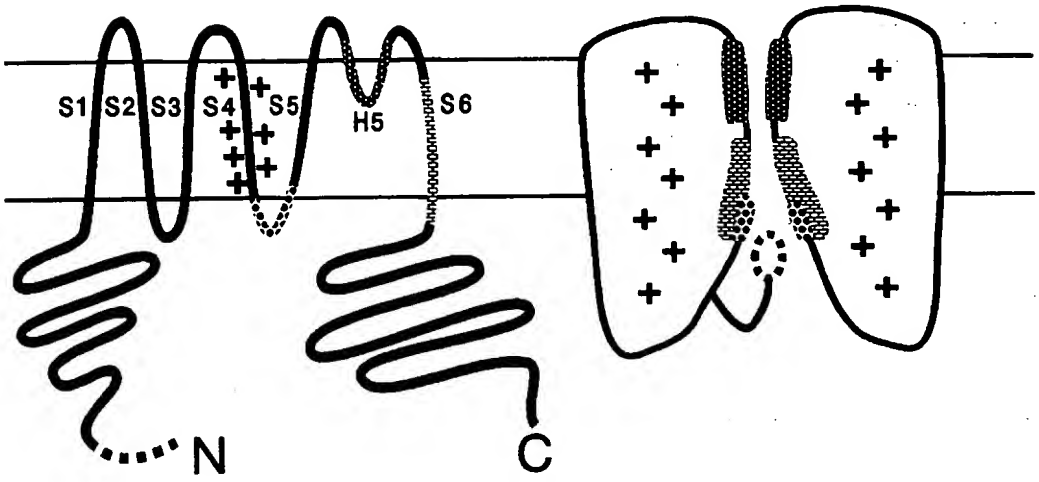

Figure 2 Structural elements of the voltage-gated potassium channel include the N-terminus as the inactivation particle, S4 as part of the voltage sensor, the S4-S5 loop that interacts with the inactivation particle, and the H5 and S6 segments as part of the permeation pathway.

et al 1994a), and the H5 or P segment that interacts with peptide toxins from the extracellular side of the membrane (Hartmann et al 1991, Kavanaugh et al 1991, Yellen et al 1991, Yool & Schwarz 1991, Heginbotham et al 1994).

Blocking of the channel pore by scorpion peptide toxins from the extracellular side of the membrane has been used to characterize the outer mouth of the channel pore as the toxin-binding surface (Miller 1995). Reiterative cycles of mutations of the channel and the toxin have identified contacts between the peptide toxin of known structure and the channel (Aiyar et al 1995, Hidalgo & Mackinnon 1995, Gross & MacKinnon 1996, Naranjo & Miller 1996, Ranganathan et al 1996). These studies indicate that the H5 segment extends into the channel pore by less than one nanometer (Lü & Miller 1995, MacKinnon 1995, Miller 1995, Ranganathan et al 1996). Similar arrangements of pore loops are likely to be found in the inwardly rectifying potassium channel that is distantly related to the voltage-gated potassium channel (Kubo et al 1993a), and in glutamate receptors that have been proposed to contain an inverted module related to the pore-forming region of potassium channels (Wo & Oswald 1995) (Figure 3).

Voltage-Dependent Activation

For a channel to sense membrane potential it has to contain charges or dipoles in the hydrophobic membrane interior. These voltage sensors detect changes in membrane potential and trigger conformational changes of the channel protein, thereby generating gating currents and causing the channel to be activated for ion permeation (Armstrong & Bezanilla 1973, Bezanilla & Stefani 1994, Sigworth

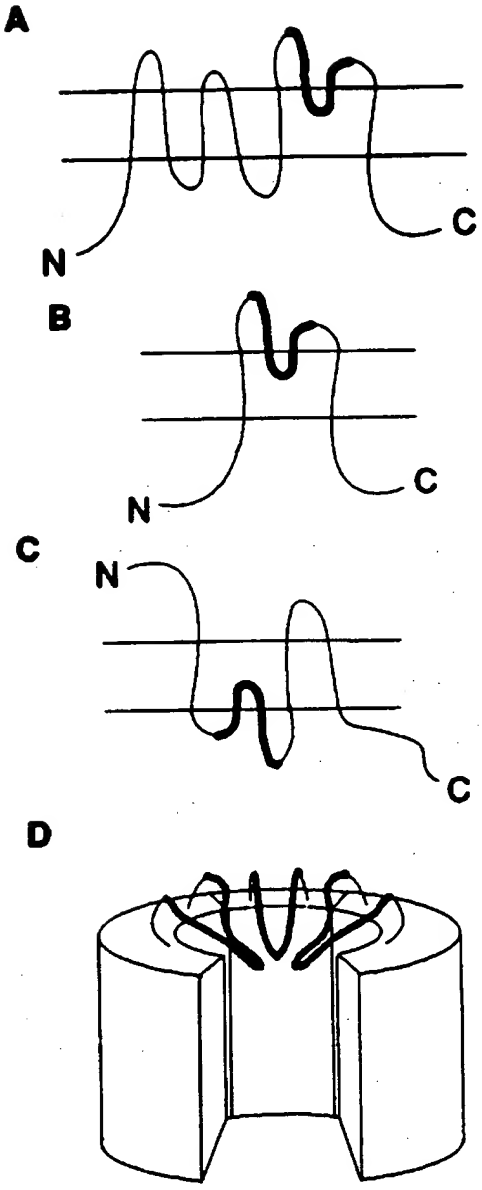

Figure 3 Pore loops form ion-channel selectivity filters. Several different ion channels contain pore loops, short polypeptide segments that loop into the ion conduction pore from one side of the membrane. Pore loop regions are shown in bold on the membrane topology diagrams. The extracellular side of the membrane is on top in each panel. (*A*) Voltage-gated potassium and cyclic nucleotide-gated channel subunits probably contain six membrane-spanning segments, with a pore loop between the fifth and sixth. (*B*) Inwardly rectifying potassium channels and ATP-gated cation channels are thought to contain two membrane-spanning segments per subunit straddling a pore loop. (*C*) Glutamate receptor ion-channel subunits probably contain a pore loop between the first and second membrane-spanning segments. (*D*) Model of a voltage-gated potassium channel with integral membrane subunits arranged like the staves of a barrel around a central ion conduction pore. One subunit has been removed in the tetramer shown. Pore loops enter into the pore to form an active site where selective ion coordination occurs. The pore loops may contain secondary structures over part of their length, but they expose loops inside the pore. (From MacKinnon 1995.)

1994). The S4 sequence, which contains positively charged basic residues at every third position and is present in voltage-gated sodium, calcium, and potassium channels, has been proposed to serve as a voltage sensor. The S4 segment spans the membrane in the *Shaker* voltage-gated potassium channel (Larsson et al 1996) and in the cyclic nucleotide-gated cation channels, which belong to the same superfamily as voltage-gated channels (Jan & Jan 1990, Henn et al 1995, Finn et al 1996). Movements of the S4 segment have been correlated with the gating currents, as described below.

Channel activation is accompanied by the translocation across the membrane of over ten charges that are intrinsic to the channel (Bezanilla & Stefani 1994, Sigworth 1994). How might this extraordinary charge movement take place? The membrane at the site of the charge translocation appears to be unexpectedly thin. Surprisingly few S4 residues (at most five, including only one basic residue) are buried in the membrane and inaccessible to the aqueous solution on either side of the membrane when the *Shaker* potassium channel is closed (Larsson et al 1996). Upon channel activation, this S4 basic residue moves outward into the aqueous phase, whereas a segment containing three or four basic residues moves from the cytoplasmic side into the membrane and becomes inaccessible to aqueous solutions (Larsson et al 1996) (Figure 4).

The movement of the S4 residues correlates temporally with the displacement of the gating charge in gating current measurement (Mannuzzu et al 1995). The S4 basic residue that is buried when the channel is closed interacts with two acidic residues in the S2 and S3 segments (Papazian et al 1995). A major component of the gating charge is contributed by the first two S4 basic residues that move from the cytoplasmic side into the membrane upon channel activation, as well as the acidic residue in the S2 segment (Seoh et al 1996). A similar translocation of S4 residues has been observed for the voltage-gated sodium channel (Yang et al 1996).

Membrane potential and internal calcium both play roles in the activation of calcium-activated potassium channels with large conductance (the maxi K channels) (Meech 1978, Barrett et al 1982). Voltage sensitivity is conferred by the core domain, which shares sequence similarity with voltage-gated potassium channels, whereas calcium sensitivity is associated with the carboxyl terminal domain (Wei et al 1994).

Inactivation Mechanisms

Once the voltage-gated potassium channel is activated by depolarization, how long the channel remains open to ion flow depends partly on inactivation mechanisms (Connor & Stevens 1971). Two mechanisms, N-type and C-type inactivation, involve structural elements in the N- and C-terminal regions of the *Shaker* potassium channel α subunit, respectively. N-type inactivation involves

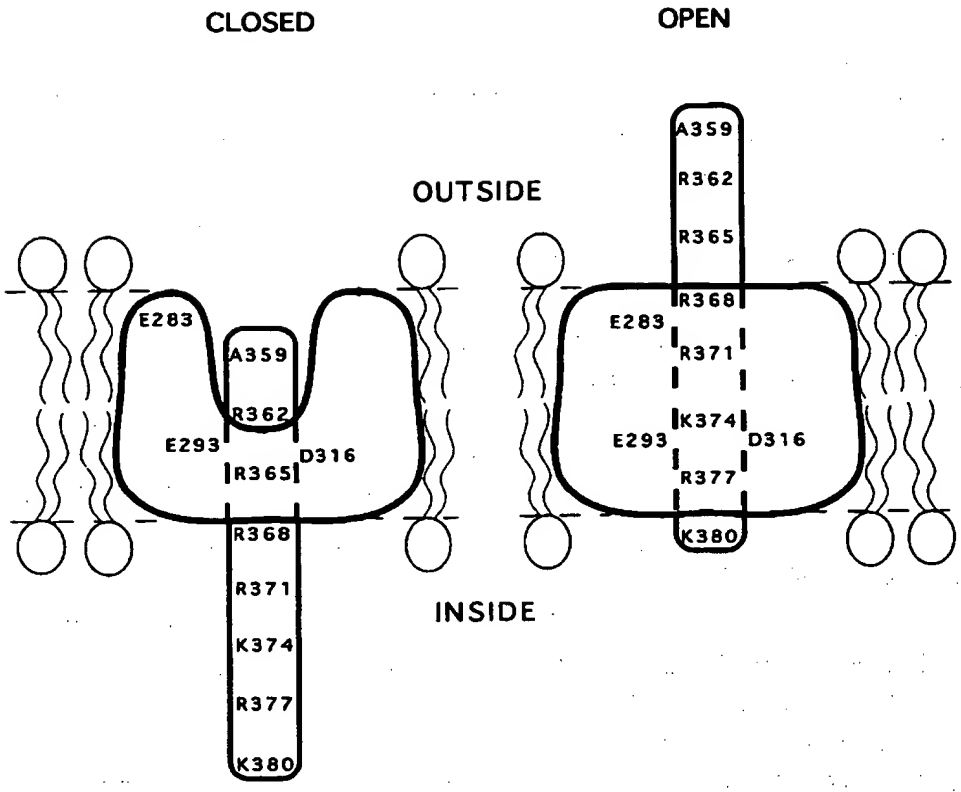

Figure 4 Transmembrane movement of the *Shaker* S4. The diagrams depict a region of protein around the S4 region of a single subunit of the *Shaker* channel in the conformations associated with the channel's closed and open states. Five residues (363–367) span the distance between the intracellular and extracellular solutions in closed channels, leaving only one basic residue buried (R365). This distance is shown as 50% of the thickness of the bilayer hydrocarbon core (about 25–30 Å), or intermediate between that spannable by an α helix (8 Å) and a β sheet (18 Å) (Stryer 1988). A crevice permits but restricts access to 359 and 362 from the external solution in the closed state. When channels open, S4 moves outward as a unit. This movement of S4, or a subsequent conformational change, closes the crevice, leaving a total of 12 residues buried (experiments show the number to be between 9 and 15). The basic residues buried in the open state form salt bridges with acidic residues in S2 and S3, as implied by Papazian et al's (1995) findings. (From Larsson et al 1996.)

a ball-and-chain mechanism (Bezanilla & Armstrong 1977) in which the N-terminus of each of the four channel subunits functions as an independent inactivation particle and occludes the cytoplasmic end of the channel pore after channel opening, thereby causing inactivation (Hoshi et al 1990, Zagotta et al 1990, MacKinnon et al 1993). The N-terminal peptide from *Shaker* also interacts with the internal mouth of the maxi K calcium-activated potassium channel, suggesting structural similarities between the pores of these channels (Toro et al 1994).

C-type inactivation can take place in the absence of N-type inactivation and appears to affect the outer mouth of the channel pore (Choi et al 1991, Hoshi

et al 1991, Lopez-Barneo et al 1993). Indeed, cysteine substitution of an H5 residue predicted to be at the outer mouth of the channel pore leads to disulfide cross-linking of two *Shaker* subunits in the C-type inactivated state but not in the closed state, revealing conformational changes that accompany C-type inactivation (Liu et al 1996).

The conformational change leading to C-type inactivation appears to take place when the potassium-binding site at the outer mouth of the channel pore is vacant (Baukrowitz & Yellen 1995, 1996). C-type inactivation is faster and more pronounced in the presence of N-type inactivation, because the channel pore is maintained in the open configuration during N-type inactivation but is not conducting, making it more likely for the potassium-binding site at the outer mouth of the pore to become unoccupied (Baukrowitz & Yellen 1995). The exit rate for potassium from the outer mouth of the pore is 100,000 ions per second when the channel pore is occluded by the inactivation particle or quarternary ammonium blockers; this rate is two orders of magnitude lower than the rate of potassium permeation, presumably because the presence of multiple potassium ions in the permeating pore speeds up dissociation of potassium ions from their binding sites (Baukrowitz & Yellen 1996).

The dependence of C-type inactivation on the presence of potassium at the outer mouth of the pore may account for the ability of external potassium concentrations to affect potassium channel activity, and the interaction between N-type and C-type inactivation would result in frequency-dependent cumulative inactivation (Baukrowitz & Yellen 1995). Because electrical activities of neurons could lead to frequency-dependent cumulative inactivation as well as changes of potassium concentrations in the extracellular space, it is expected that the activities of voltage-gated potassium channels are modulated by prior neuronal activities. For example, an unusually pronounced form of C-type inactivation allows the voltage-gated potassium channel encoded by the HERG gene to exhibit inward rectification as well as to increase potassium efflux during the initiation of a premature heart beat (Smith et al 1996); this could explain why cardiac sudden death may result from mutations of the HERG gene (Sanguinetti et al 1995) or treatment with class III antiarrhythmic drugs that block HERG channels (Kiehn et al 1995).

The β Subunits

Four mammalian β subunit sequences have been reported: Kvβ1.1, Kvβ1.2, and Kvβ1.3 (resulting from alternative splicing of a single gene), and Kvβ2.1 (resulting from a related gene) (England et al 1995a, McCormack et al 1995). Kvβ1.1 enhances N-type inactivation of Kv1.4 and the *Drosophila Shaker* potassium channel because its N-terminus functions as an inactivation particle (Rettig et al 1994, Yu et al 1996). Kvβ1.2 and Kvβ1.3 also accelerate

N-type inactivation and, directly or indirectly, affect C-type inactivation, voltage dependence of activation, and the rate of deactivation (Castellino et al 1995; England et al 1995a,b; Majumder et al 1995; Rasmusso et al 1995). Kvβ2.1 complexes with Kv1.2 in vivo and with Kv1.5 in L-cells transfected with Kv1.5 (Scott et al 1994, Uebele et al 1996). It accelerates N-type inactivation of Kv1.4, increases C-type inactivation of Kv1.5, and causes channel activation to occur at more hyperpolarized potentials (Uebele et al 1996). Although the effects of β subunits on channel properties appear to vary with the α subunits present in the channel, interaction between the β subunit and the *Shaker* α subunit involves the conserved C-terminal domain of the β subunit and the conserved N-terminal hydrophilic domain of the α subunit, the same region involved in the interaction and the determination of compatibility between α subunits (Nakahira et al 1996, Sewing et al 1996, Yu et al 1996).

A β subunit of related sequence (48% identity with Kvβ2.1) and similar function is encoded by the *Hyperkinetic* gene in *Drosophila*, accounting for its *Shaker*-like ether-sensitive leg-shaking and neuromuscular transmission phenotype (Chouinard et al 1995). The known β subunit sequences show significant similarity to members of the NAD(P)H-dependent oxidoreductase superfamily (McCormack & McCormack 1994).

Unlike the β subunits of voltage-gated potassium channels, the β subunit of the maxi K calcium-activated potassium channel contains two putative transmembrane segments (Knaus et al 1994). This subunit increases the apparent calcium sensitivity of the channel. The functional coupling between the α and the β subunits is in turn regulated by internal calcium (Meera et al 1996).

Channel Regulation

Differential expression of voltage-gated potassium channel subunits in different subcellular compartments of various neurons indicates that the channel proteins in the cell body are likely to differ from those present in the dendrites or axon terminals (Hwang et al 1993, Goldman-Wohl et al 1994, Maletic-Savatic et al 1995, Rhodes et al 1995, Weiser et al 1995, Knaus et al 1996). Indeed, heteromultimeric channel complexes that share some, but not all, of the subunits appear to be targeted to different subcellular compartments (Sheng et al 1993, Wang et al 1993). Although it is unknown how different channels are targeted to highly specialized compartments such as axon terminals and the juxtaparanodal regions flanking the nodes of myelinated axons, physical interactions between *Shaker*-type (Kv1) voltage-gated potassium channels and PSD-95 or other members of the membrane-associated putative guanylate kinase family have been found to cause clustering of these potassium channels (E Kim et al 1995), indicating that such protein-protein interaction may be important for positioning potassium channels at sites in the vicinity of the synapse.

Expression and function of voltage-gated potassium channels are regulated by a variety of mechanisms. Phosphorylation of specific residues by protein kinases has been found to affect current amplitude, voltage dependence or kinetic properties of the channel (Huang et al 1993, Covarrubias et al 1994, Esguerra et al 1994, Huang et al 1994, Moreno et al 1995, Holmes et al 1996), and direct actions of arachidonic acid and other unsaturated fatty acids appear to suppress Kv1.5 and members of the Kv4 subfamily (Honoré et al 1994, Villarroel & Schwarz 1996). Transcription regulation of Kv1.5 shows remarkable responsiveness to neuronal activities and neurotransmitters (Levitan et al 1995, Takimoto et al 1995). Glucocorticoid induction of the Kv1.5 gene has been observed in cardiac and pituitary cells (Attardi et al 1993, Takimoto & Levitan 1994), and the cell type-specific expression may involve a silencer element (Mori et al 1995). Instead of regulation at the transcriptional level, the up-regulation of Kv2.1 by nerve growth factor appears to involve an increase and redistribution of the protein product (Sharma et al 1993).

INWARDLY RECTIFYING POTASSIUM CHANNELS

Inwardly rectifying potassium channels allow potassium ions to enter the cell much more readily than does potassium permeation in the opposite direction, regardless of the potassium concentration in the external solution and hence of the potassium equilibrium potential (Hagiwara et al 1976). Thus, inwardly rectifying potassium channels appear to be sensitive to the electrochemical driving force for potassium ions. These channels play a significant role in determining the resting potential of a cell and may be regulated by hormones, neurotransmitters, and the cell's internal metabolic state (Hille 1992). Recent cloning of at least twelve inwardly rectifying potassium channel genes (Doupnik et al 1995) with distinct patterns of expression in the mammalian brain and other tissues (Bredt et al 1995, Karschin et al 1996, Ponce et al 1996, Spauschus et al 1996) has revealed that these channels are distantly related to voltage-gated potassium channels (see Figure 1), and has led to further analysis of gating mechanisms underlying inward rectification and channel regulation via G-protein-coupled receptors or cytoplasmic ATP.

Potassium Permeation and Inward Rectification Gating

The observed dependence of inward rectification gating on the driving force for potassium ions could be accounted for by a block of the channel pore by cytoplasmic cations such as magnesium and polyamines (Matsuda et al 1987, Vandenberg 1987, Ficker et al 1994, Lopatin et al 1994, Fakler et al 1995). Magnesium and putrecine can account for instantaneous rectification, whereas spermidine and spermine, polyamines that carry more positively charged amine

moieties than putrecine, cause slower rectification (Lopatin et al 1995, Yamada & Kurachi 1995, Ishihara et al 1996). Inhibition of S-adenosylmethionine decarboxylase reduces spermidine and spermine levels as well as inward rectification of an inwardly rectifying potassium current in basophilic leukemia cells (Bianchi et al 1996), indicating that the extent of inward rectification is determined partly by the polyamine concentrations in vivo. Inward rectification gating is a function of the driving force for potassium ions when the external potassium concentration is varied, but not when the internal potassium concentration is altered, probably because the cytoplasmic blocking cation can be repelled by potassium occupying an external potassium-binding site in the long pore (Hagiwara & Yoshii 1979, Matsuda 1991, Kubo 1996).

Given the extrinsic gating of inwardly rectifying potassium channels by cytoplasmic cations, it is not surprising that mutations affecting potassium permeation also affect inward rectification and the channel block by magnesium and polyamines. A mutation of the conserved glycine in the H5 segment of GIRK2 abolishes potassium selectivity (Slesinger et al 1996), as does the analogous mutation in the *Shaker* H5 segment (Heginbotham et al 1994). Similar to the involvement of the last hydrophobic segment of the voltage-gated potassium channel α subunit in potassium permeation (Lopez et al 1994), the M2 segment of the inwardly rectifying potassium channel harbors a residue important for potassium selectivity; this residue also affects channel blocking by magnesium and polyamines from the cytoplasmic side as well as channel blocking by strontium from the extracellular side of the membrane (Lu & MacKinnon 1994, Stanfield et al 1994, Wible et al 1994, Reuveny et al 1996). This residue is likely to be exposed to the aqueous solution from the cytoplasmic side. It affects selectivity of the channel for internal potassium and rubidium ions (Reuveny et al 1996), and histidine substitution at this position results in a mutant channel whose inward rectification varies with internal pH (Lu & MacKinnon 1995).

Whereas the weak similarity between the hydrophobic domain of the inwardly rectifying potassium channel α subunit and the second half of the voltage-gated potassium channel α subunit suggests that multiple regions of the hydrophobic domain are involved in potassium permeation, the hydrophilic C-terminal domain of a strongly rectifying potassium channel contains an acidic residue that is also important for potassium permeation and inward rectification (Taglialatela et al 1994b, 1995; Yang et al 1995a), raising the question as to whether the inwardly rectifying potassium channel has a pore that extends further into the cytoplasm than the pore of voltage-gated potassium channels (Figure 5). Like voltage-gated potassium channels, inwardly rectifying potassium channels are tetramers (Inanobe et al 1995, Yang et al 1995b). Tetrameric channels containing only one subunit with high sensitivity to polyamines still show high sensitivity (one sixth that of homotetramers),

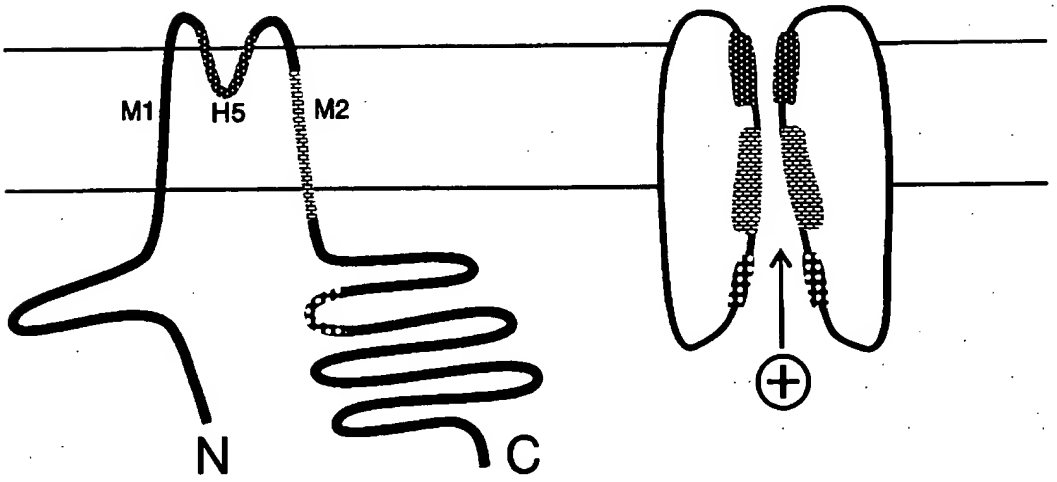

Figure 5 Structural elements of an inwardly rectifying potassium channel include the H5 and M2 segments and part of the C-terminal hydrophilic domain as part of the permeation pathway.

indicating that the blocking cation interacts primarily with one of the four pore-forming subunits (Yang et al 1995b).

Channel Regulation by ATP

Certain members of the inwardly rectifying potassium channel family are inhibited by cytoplasmic ATP and non-hydrolyzable analogs of ATP. This mechanism of channel regulation by the cell's internal metabolic state has been used to control vascular tone, insulin release from pancreatic β cells, potassium flow in kidney cells, as well as to protect against hypoxia (Ashcroft 1988, Nichols & Lederer 1991, Ben-Ari et al 1992, Jiang et al 1994, Giebisch 1995, Nelson & Quayle 1995, Terzic et al 1995, Seino et al 1996).

Sulfonylureas, which have been used in the treatment of diabetes, inhibit some of these ATP-sensitive potassium channels as well as other types of potassium channels (Ashcroft 1988, Crépel et al 1993). Recent studies indicate that the ATP-sensitive potassium channels from pancreatic β cells contain at least two types of subunits, the pore-forming subunit (Kir6.2) that belongs to the family of inwardly rectifying potassium channels and the sulfonylurea receptor that belongs to the ABC (ATP-binding cassette) family (Aguilar-Bryan et al 1995, Inagaki et al 1995, Sakura et al 1995, Seino et al 1996).

Whereas ATP-sensitive potassium channels in the pancreas show high sensitivity to ATP and sulfonylurea agents such as glibenclamide, ATP-sensitive potassium channels in the kidney are much less sensitive; their sensitivity to sulfonylureas may be derived from the association of the pore-forming subunits (ROMK2 or Kir1.1b) with CFTR (cystic fibrosis transmembrane regulator), an ABC family member highly expressed in the nephron (Giebisch 1995,

McNicholas et al 1996a). The ATP-sensitivity could reside in the ABC family member (Seino et al 1996). Alternatively, a putative Walker A site for ATP-binding in the C-terminal hydrophilic domain of ROMK2 may provide nucleotide sensitivity (McNicholas et al 1996b).

Channel Regulation by the G-Protein

Transmitter activation of G-protein-coupled receptors often leads to regulation of inwardly rectifying potassium channels (Hille 1992, 1994; Nakajima & Nakajima 1994; Kurachi 1995; Wickman & Clapham 1995a,b). The first demonstration of chemical transmission, calming of the heart rate by parasympathetic stimulation (Loewi 1921), resulted from activation of the muscarinic cholinergic receptor and the subsequent activation of an inwardly rectifying potassium channel (the muscarinic potassium channel) (Kurachi 1995, Wickman & Clapham 1995a,b). In the central nervous system, similar inwardly rectifying potassium channels may be subjected to activation resulting from the action of inhibitory transmitters such as acetylcholine, GABA, somatostatin, opioid peptides, and adenosine, as well as suppression resulting from the action of excitatory transmitters such as neurotensin and substance P (North 1989, Nicoll et al 1990, Farkas et al 1994, Nakajima & Nakajima 1994, Premkumar & Gage 1994, KM Kim et al 1995, Velimirovic et al 1995, Grigg et al 1996, Sodickson & Bean 1996). Channel activation mediated by G-protein-coupled receptors for transmitters may arise from a direct action of the G protein.

Activation of the muscarinic potassium channel by cholinergic stimulation of the cardiac muscarinic receptor does not involve diffusible cytoplasmic second messengers (Sakmann et al 1983, Soejima & Noma 1984). This membrane-delimited pathway of channel activation is mediated by the G-protein (Breitwieser & Szabo 1985, Pfaffinger et al 1985), probably the $\beta\gamma$ subunit (Logothetis et al 1987, Reuveny et al 1994, Wickman et al 1994, Yamada et al 1994, Kofuji et al 1995, Nair et al 1995).

The muscarinic potassium channel from the atrium is probably formed by two members of the inwardly rectifying potassium channel family, GIRK1 and GIRK4 (Kir3.1 and Kir3.4) (Dascal et al 1993, Kubo et al 1993b, Duprat et al 1995, Krapivinsky et al 1995a). Both the N- and C-terminal hydrophilic domains of GIRK1 bind directly to the $\beta\gamma$ subunit of the G-protein, and such direct protein-protein interactions are important for channel activation (Huang et al 1995) (Figure 6). Binding of the $\beta\gamma$ subunit to GIRK4 has also been observed and could also contribute to channel activation (Krapivinsky et al 1995b).

The N- but not the C-terminal hydrophilic domain of GIRK1 also binds the inactive α-GDP subunit and the trimeric G-protein (Huang et al 1995). This observation correlates with the ability of the N- but not the C-terminal

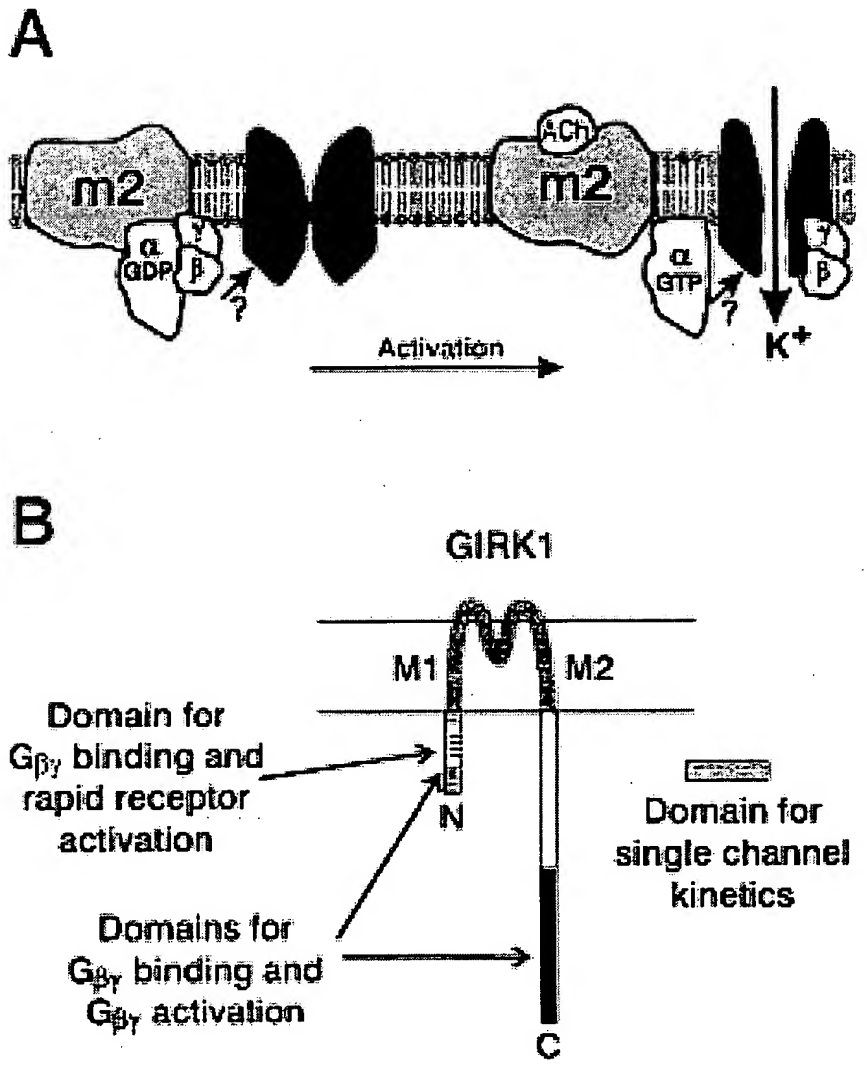

Figure 6 Proposed mechanism for G-protein activation of muscarinic potassium channel. (*A*) Activation of the GIRK1 channel following muscarinic stimulation. At rest, the muscarinic receptor, inactive G-protein heterotrimer ($G_{\alpha\beta\gamma}$), and the GIRK1 channel may form a local complex that is specified, in part, by the binding interaction of the G-protein with the GIRK1 channel. In this scenario, because the channel is situated near the receptor-G-protein complex, the channel is exposed to a high local concentration of free $G_{\beta\gamma}$ subunits upon receptor stimulation, thereby enabling rapid activation of the channel. The interaction of the channel with the activated G_{α}-GTP may accelerate the GTPase activity of the G_{α}-GTP, promoting rapid deactivation at the end of receptor stimulation (Breitwieser & Szabo 1988). (*B*) Functional domains implicated in G protein activation of GIRK1. The hydrophobic domain (M1-H5-M2) of GIRK1 contains a gate governing the single-channel openings. The N- and C-terminal hydrophilic domains of GIRK1, in contrast, contain regions important for the $G_{\beta\gamma}$ binding (Huang et al 1995) and $G_{\beta\gamma}$ activation of the GIRK1 channel. The N-terminal domain of GIRK1 also facilitates the rapid activation following receptor stimulation and binds the $G_{\alpha\beta\gamma}$ heterotrimer (Huang et al 1995). (From Slesinger et al 1995.)

hydrophilic domain of GIRK1 to enable chimeric channels to be activated rapidly upon muscarinic receptor stimulation (Kunkel & Peralta 1995, Slesinger et al 1995).

Given that the muscarinic potassium channels can be activated by various isoforms of the $\beta\gamma$ subunits (Wickman et al 1994), why are only a subset of the G-protein-coupled receptors of a cell capable of activating these channels in vivo? One way to ensure the specificity of receptor actions might be the compartmentalization of the receptor, the G-protein, and the channel, potentially involving interactions among these proteins (Huang et al 1995, Slesinger et al 1995).

Similar to the muscarinic potassium channels in the heart and related channels in central neurons, neuronal voltage-gated calcium channels may be modulated by the $\beta\gamma$ subunit (Ikeda 1996, Herlitze et al 1996). By contrast, ATP-sensitive potassium channels in the heart may be stimulated by the activated α subunit of the G-protein, probably because of an antagonistic effect between the G-protein subunit and ATP (Terzic et al 1994).

POTASSIUM CHANNELS IN DIFFERENT KINGDOMS

Kv-like potassium channel sequences have been found not only in the animal kingdom but also in plants, protists, and prokaryotes (Schachtman et al 1992, Sentenac et al 1992, Milkman 1994, Jegla & Salkoff 1995, Jegla et al 1995, Müller-Röber et al 1995). Among these sequences is a cGMP-gated potassium channel that shares structural motifs with both the *Shaker* potassium channel and cyclic nucleotide-gated cation channels (Yao et al 1995) (Figures 7 and 8). Other sequences include a prokaryotic potassium channel resembling Kir (Schrempf et al 1995), a mammalian potassium channel that contains two Kir-like hydrophobic domains (Lesage et al 1996b), as well as yeast and *Caenorhabditis elegans* potassium channel sequences that contain one Kv-like hydrophobic domain followed by one Kir-like hydrophobic domain (Ketchum et al 1995, Zhou et al 1995, Lesage et al 1996a, Reid et al 1996) (Figures 7 and 8). In this section we summarize the known properties of these potassium channels or potassium channels/transporters (potassium transport systems that have not been shown to be channels), their potential functional roles, and tantalizing hints of potential conservation of β subunits as well as the pore-forming α subunits of potassium channels.

Metazoan Voltage-Gated Potassium Channels

Triploblastic metazoans such as vertebrates, arthropods, mollusks, and nematodes contain at least four subfamilies of voltage-gated potassium channels (*Shaker*, *Shab*, *Shaw*, *Shal*) (Pfaffinger et al 1991, Salkoff et al 1992, Zhao

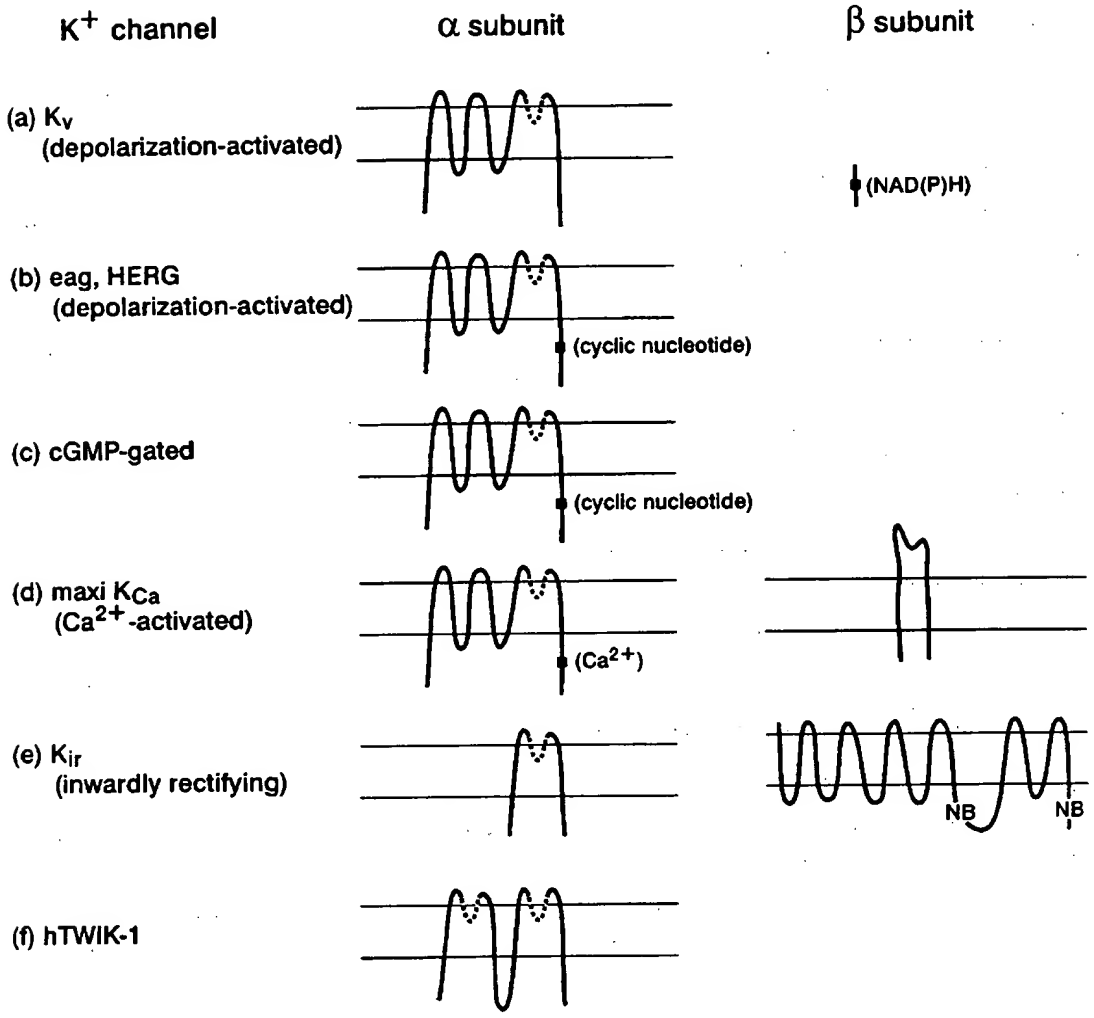

Figure 7 Potassium channels in the animal kingdom. Proposed membrane topology of known α and β subunits and motifs for binding NAD(P)H, cyclic nucleotide, or calcium are shown. Double lines indicate the cell membrane; the cytoplasmic side is below the membrane. NB, nucleotide binding domain. (*a*) Chandy & Gutman 1995, Scott et al 1994; (*b*) Curran et al 1995; (*c*) Yao et al 1995; (*d*) Wei et al 1994, Knaus et al 1994; (*e*) Doupnik et al 1995, Aguilar-Bryan et al 1995; (*f*) Lesage et al 1996b.

et al 1994, Baro et al 1996). The diploblast jellyfish, among the most ancient extant metazoans to have true nervous systems, also contain multiple potassium channel genes; the two known genes are about 50% identical to each other and to *Shaker* (Jegla et al 1995). These channels may provide a direct link to specific behaviors of the jellyfish (Meech & Mackie 1993, Przysiezniak & Spencer 1994).

In contrast to potassium channel sequences that each contain a single Kv-like or Kir-like hydrophobic domain, a human potassium channel sequence has two Kir-like hydrophobic domains. It gives rise to potassium channels that

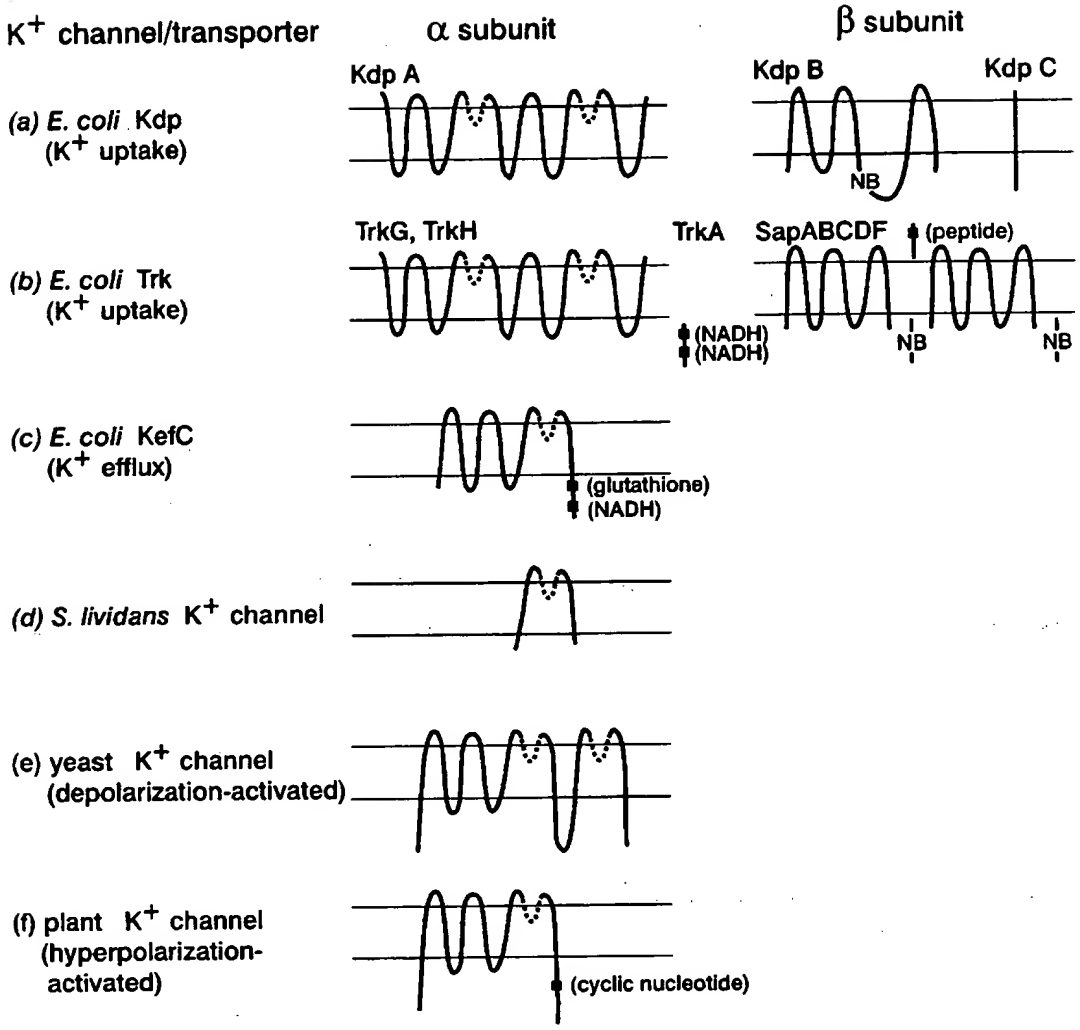

Figure 8 Potassium channels/transporters in bacteria, yeast, and plants. Proposed membrane topology of known α and β subunits and motifs for binding NADH, glutathione, and cyclic nucleotide are shown. NB, nuceotide binding domain. The SapABCDF peptide transporter in *Salmonella typhimurium* is the homolog of TrkE in *Escherichia coli*. (*a*) Hesse et al 1984, Buurman 1995; (*b*) Bakker 1993, Schlösser et al 1993, Parra-Lopez et al 1994; (*c*) Schleyer & Bakker 1993; (*d*) Schrempf et al 1995; (*e*) Ketchum et al 1995, Zhou et al 1995; (*f*) Anderson et al 1992, Sentenac et al 1992.

show magnesium-dependent weak inward rectification and is abundant in brain and heart, indicating that it could contribute to the resting potential and to the background potassium conductance of excitable cells (Lesage et al 1996b).

Plant Voltage-Gated Potassium Channels

Potassium, together with nitrogen and phosphate, is one of the three main macronutrients administered in fertilizers. It is the most abundant cellular

cation in plants, and its transport across the cell membrane is important for germination, growth, nutrient transport and storage, leaf movement, and regulation of stomatal aperture (Assmann 1993, Blatt & Thiel 1993, Schroeder et al 1994). Potassium uptake into roots and potassium influx into guard cells, with consequent swelling of the guard cells and stomatal pore opening, is mediated partly by inwardly rectifying potassium channels. The inward rectification of these channels is independent of intracellular magnesium blocking and, thus, differs mechanistically from the gating of inward rectifiers in the animal kingdom. Additional evidence indicates that these plant channels are gated by voltage. The plant inwardly rectifying potassium channels resemble voltage-gated potassium channels in having six hydrophobic segments and an H5 segment (Anderson et al 1992, Schachtman et al 1992, Sentenac et al 1992, Müller-Röber et al 1995) (Figure 8). Moreover, chimeras of plant and animal channels (*Xenopus Shaker*) that contain the first third of the plant channel sequence, including the first four hydrophobic segments (S1–S4), are activated by hyperpolarization (Cao et al 1995). Thus, the membrane topology of these plant channels is likely to resemble that of voltage-gated potassium channels in the animal kingdom; their activation by hyperpolarization rather than depolarization is probably the result of differences in the channel gating machinery.

Channel regulation by hormones and other external or internal stimuli is well known in plants (Assmann 1993, Blatt & Thiel 1993, Schroeder et al 1994). The plant hormone auxin couples various environmental and developmental signals to the control of solute transport and may inhibit inwardly rectifying potassium channels in the guard cell by altering internal pH (Thiel et al 1993). Abscisic acid, which signals conditions of water stress, also causes inhibition of inwardly rectifying potassium channels and stomatal closure by a second messenger pathway that requires protein phosphatase (Li et al 1994, Schwartz et al 1994, Armstrong et al 1995). Plant potassium channels may also be regulated by the G-protein, sometimes via membrane-delimited pathways; however, the signals (e.g. light, hormones) that activate such G-protein-mediated pathways of channel regulation are unknown (Li & Assmann 1993, Wu & Assmann 1994, Armstrong & Blatt 1995).

Yeast Potassium Channels

The budding yeast *Saccharomyces cerevisiae* has been used in the cloning and functional analysis of potassium channels. Two genes required for high- and low-affinity potassium transport encode proteins that contain multiple hydrophobic segments and resemble ABC transporters; removal of these gene functions eliminates the small, fast-activating inwardly rectifying potassium current (Bertl et al 1995). Although it is unknown whether these yeast gene products function as potassium channels, double mutant yeast strains deficient

for these potassium transport systems can be complemented for growth in low potassium medium by animal or plant inwardly rectifying potassium channels (Anderson et al 1992, Sentenac et al 1992, Tang et al 1995), a high-affinity potassium uptake transporter from the ascomycete yeast *Schwanniomyces occidentalis* in the soil (Bañuelos et al 1995), as well as a sodium-driven high-affinity potassium uptake transporter from the plant (Rubio et al 1995). These mutants also allow for large-scale genetic screens for mutations that alter channel functions such as ion selectivity or conductance (Anderson et al 1994, Uozumi et al 1995). The depolarization-activated potassium channel gene of the budding yeast has emerged from the Yeast Genome Sequencing Project and encodes a protein containing a Kv-like as well as a Kir-like hydrophobic domain (Ketchum et al 1995, Zhou et al 1995, Lesage et al 1996a, Reid et al 1996) (Figure 8).

Prokaryotic Potassium Channels/Transporters

Potassium, next to sodium, is the second most abundant alkali cation in nature and is concentrated in all cells. This concentration could have arisen because potassium has a larger radius and lower hydration energy, thereby allowing it to preferentially partition into the cytoplasm (Wiggins 1990). Alternatively, exclusion of sodium from the cytoplasm may have been adopted by cells as a means to drive transport of other ions and solutes via the electrochemical sodium gradient, leaving potassium to be accumulated by cells in order to develop a negative turgor pressure (Epstein 1986, Bakker 1993). The prokaryotic potassium transport systems that have been characterized genetically and molecularly (Figure 8) offer intriguing hints to the origin of the potassium channels in eukaryotes. Although the efficiency of some of these systems approaches that of ion channels (Munro et al 1991, Bakker 1993), it is unknown whether the prokaryotic potassium transport proteins function as channels; hence, they are referred to as potassium channels/transporters.

Several potassium uptake systems are used by *E. coli* and other bacteria (Dorsch et al 1991, Bakker 1993) (Figure 8). The P-type potassium translocating Kdp-ATPase (Hesse et al 1984), including the catalytic KdpB subunit and the hydrophobic KdpA subunit unique to this P-type ATPase, is induced by low turgor pressure and transports potassium with a high affinity (Km is about 2 μM). The low-affinity TrkG/H system allows for potassium uptake from media containing at least 1 mM potassium. The system is constitutively active and can be activated further by low turgor pressure, and it includes the following gene products: TrkA, TrkE, and TrkG/H.

TrkG and its functionally equivalent homolog, TrkH, are integral membrane proteins, as is KdpA. TrkG and KdpA appear to each contain two motifs with limited sequence similarity to the M1-H5-M2 hydrophobic domain of inwardly rectifying potassium channels or the S5-H5-S6 region of voltage-gated

potassium channels (Jan & Jan 1994). Mutations that reduce the potassium affinity for the Kdp potassium transport system fall into three extracellular loops of the KdpA protein with ten transmembrane segments, including the two H5-like segments (corresponding to the following underlined H5 residues of *Shaker*: WWAVVTMTTVGYG), and the cytoplasmic loop that precedes the second M1/S5-like transmembrane segment and would be equivalent to the *Shaker* S4-S5 loop (see Figure 2) (Buurman et al 1995).

Further similarity between prokaryotic potassium uptake systems and eukaryotic potassium channels is suggested by a comparison between the β subunits of voltage-gated potassium channels and TrkA, and between an inwardly rectifying potassium channel β subunit that belongs to the ABC superfamily of transporters and similar ABC family members involved in prokaryotic potassium uptake as well as resistance to toxic peptides (Figures 7 and 8).

Similarities between the β subunits of eukaryotic voltage-gated potassium channels and TrkA of the prokaryotic Trk potassium transport system include their location on the cytoplasmic side of the membrane and their sequence motifs that can potentially monitor the reducing power of the cell. The TrkA protein contains two internal repeats each with an NAD(H)-binding motif, and the purified TrkA protein binds NAD(H) (Schlösser et al 1993) (Figure 8). Membrane association of TrkA requires the presence of wild-type TrkG or TrkH, and intragenic complementation suggests that more than one copy of the TrkA protein is present per Trk complex (Bossemeyer et al 1989, Bakker 1993). The eukaryotic voltage-gated potassium channel may contain four β subunits with sequence similarity to the NAD(P)H-binding domain of oxidoreductase, similar to TrkA. These β subunits are globular proteins bound to the cytoplasmic side of the pore-forming α subunits, analogous to the TrkG/H-dependent membrane association of TrkA (McCormack & McCormack 1994, Rettig et al 1994, Scott et al 1994, Sewing et al 1996, Yu et al 1996) (Figure 7).

Similarities between eukaryotic inwardly rectifying potassium channels and the prokaryotic Trk potassium transport system stem from the involvement of a potential β subunit that belongs to the ABC superfamily. Resistance of *Salmonella typhimurium* to cationic antimicrobial peptides from mammals and insects, such as protamine, melittin, and mastoparan, requires the SapABCDF operon with strong homology to ABC family transporters for uptake of small peptides; the SapABCDF transporter presumably imports these toxic peptides for subsequent inactivation (Parra-Lopez et al 1993). SapABCDF and two other genes, SapJ and SapG, are involved in peptide resistance as well as potassium transport; SapABCDF, SapJ, and SapG are true homologs of TrkE, TrkH, and TrkA of the Trk potassium transport system in *E. coli* (Parra-Lopez et al 1994, Higgins 1995). Thus, it appears that the potassium transporter TrkH/SapJ, the peptide transporter TrkE/SapABCDF, and the NAD(H)-binding protein

TrkA/SapG are in a functional complex and perhaps are subjected to coordinated regulation by the reducing power of the cell (Parra-Lopez et al 1994). Analogous to SapABCDF, the sulfonylurea receptor and CFTR belong to the ABC superfamily and are potential β subunits of certain eukaryotic inwardly rectifying potassium channels (Aguilar-Bryan et al 1995, Inagaki et al 1995, McNicholas et al 1995a).

Unlike Kdp and Trk, a third potassium uptake system, Kup in *E. coli*, is not involved in osmoadaption (Dorsch et al 1991, Bakker 1993). It is similar to (32% identity) the ascomycete yeast *Saccharomyces occidentalis* potassium transport system, which can be activated by glucose (Schleyer & Bakker 1993, Bañuelos et al 1995). The latter can substitute functionally for the potassium transport systems in the budding yeast, as do certain eukaryotic inwardly rectifying potassium channels (Anderson et al 1992, Sentenac et al 1992, Tang et al 1995).

Whereas the Kdp and Trk potassium uptake systems each contain several proteins, including three (KdpA, TrkG, TrkH) corresponding to the pore-forming α subunits and others (TrkA, TrkE/SapABCDF) bearing resemblance to various β subunits of eukaryotic potassium channels, some prokaryotic potassium efflux proteins appear to embody features of α subunits and motifs characteristic of β subunits. Two potassium efflux systems in *E. coli*, KefB and KefC, appear to be controlled by the redox state of the cell; they are inhibited by reducing agents and activated by oxidizing agents (Meury & Robin 1990, Bakker 1993). Indeed, depletion of glutathione by sulfhydryl reagents or mutations affecting glutathione synthesis increases potassium efflux (Meury & Robin 1990). The activated KefC protein allows nearly one million potassium ions to leave the cell in a second, similar to the efficiency of channels (Munro et al 1991). KefC contains five or six putative transmembrane segments in the N-terminal domain, including a segment (a.a. 111–154, 165–213) with sequence similarity to the second M1-H5-M2/S5-H5-S6 motif of KdpA (a.a. 416–506) (Munro et al 1991, Jan & Jan 1994). The C-terminal hydrophilic domain of KefC contains sequences similar to the glutathione-binding site of glyoxalase and glutathione-S-transferase, and sequences similar to the NAD(H)-binding sites in TrkA (Munro et al 1991, Parra-Lopez et al 1994) (see Figure 8). These sequence motifs indicate that gating of KefC activity by the redox state of the cell could involve binding of glutathione derivatives and/or NAD(H) to the KefC protein, which appears to include the pore-forming hydrophobic domain.

Although it is unknown whether the potassium transport systems in *E. coli* involve ion channels, potassium channels can be induced by a gene of the gram-positive soil bacterium *Streptomyces lividans*, which encodes a protein with two hydrophobic segments flanking an H5-like segment. These hydrophobic segments show the closest kinship to the S5, H5, and S6 segments of the *Shaker*

voltage-gated potassium channels (Schrempf et al 1995). This channel is about three times more permeable to potassium than sodium and appears to require internal magnesium for its activity. Removal of this channel gene results in slow growth and reduced mycelial density, thereby revealing its physiological significance (Schrempf et al 1995).

CONCLUSIONS

Potassium transport allows the accumulation of potassium in all cells. In many cases this function is fulfilled by potassium channels. Whereas diversification during evolution has led to a wide range of potassium channels for the control of volume, secretion, and electrical or chemical signaling, there may be remarkable conservation of channel function and regulation.

One potential conserved mechanism of channel regulation may be the sensitivity of channel activities to the metabolic state of a cell: energy as represented by the level of ATP or NADH, reducing power for biosynthesis as represented by the NADPH level, and glutathione for the reduction of cysteines and toxic peroxides (Stryer 1988). In *E. coli*, the constitutive potassium uptake system requires TrkA, which binds NAD(H) (Dorsch et al 1991, Bakker 1993, Schlösser et al 1993), and the constitutive potassium efflux system KefC appears to be a potassium channel gated by glutathione and possibly NADH (Meury & Robin 1990, Munro et al 1991). In heart mitochondria, potassium efflux can be activated by oxidation of NADPH (Jung & Brierley 1981). Voltage-gated potassium channels from mammals and from *Drosophila* contain β subunits with NAD(P)H-binding motifs similar to those in TrkA (McCormack & McCormack 1994, Chouinard et al 1995), thus raising the question of whether these motifs reflect a conserved machinery for channel regulation by the level of energy and/or reducing power of the cell.

Another recurring theme is the coupling between channels and ABC transporters (Parra-Lopez et al 1994, Higgins 1995, Inagaki et al 1995, McNicholas et al 1996a, Sakura et al 1995). The channels and ABC transporters could potentially regulate each other or be coordinately regulated by ATP, by NAD(H)-binding subunits such as TrkA, or by other signaling processes (Henquin 1980, Ashcroft & Kakei 1989, Duchen et al 1993, Parra-Lopez et al 1994, Higgins 1995).

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